REMARKS

Applicants appreciate the Examiner's agreement to rejoin claim 8 with the elected Group I, an agreement reached between the Examiner and Applicants' representative by telephone on September 24, 2002.

Upon entry of the above amendment, claims 11-22 will be pending in the case, claims 1, 2, and 8 having been canceled and new claims 11-22 added by the amendment. Claims 3-7, 9, and 10 have been withdrawn from consideration. Support for new claim 11 can be found, *e.g.*, on page 6, lines 8-15. Support for new claims 12 and 13 can be found, *e.g.*, on page 6, lines 16-18. Support for new claims 14-16 can be found, *e.g.*, on page 4, lines 17-22, and on pages 6-7, lines 23-2. Support for new claim 17 can be found, *e.g.*, on page 4, lines 1-4, and page 10, lines 4-6 and 11-15. Support for new claims 18-20 can be found, *e.g.*, on page 4, lines 17-22, on pages 6-7, lines 23-2, and on page 11, lines 4-9. Support for claims 21 and 22 can be found, *e.g.*, on page 9, lines 28-30. The title has been amended according to the Examiner's suggestion on page 3 of the Office action. No new matter has been added.

35 U.S.C. §112, second paragraph

Claims 1, 2, and 8 are rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. The Examiner states on pages 3-4 of the Office action:

> Claims 1 and 2 are indefinite over the recitation "determining the sequence of the nucleic acid of the human at position..." and claim 8 is indefinite over the recitation "determining the sequence of the nucleic acid at one or more of position..." because it is unclear how you determine a sequence at a single position of a nucleic acid..,Claims 1, 2, and 8 are further indefinite over the recitation "determining the status of the human by reference to polymorphism" because it is not clear what this step is requiring.

Applicants have canceled claims 1, 2 and 8, rendering this rejection moot. New claims 11-22 do not contain the objected-to language. Applicants therefore request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

35 U.S.C. §112, first paragraph

Claims 1, 2, and 8 are rejected under the first paragraph of 35 U.S.C. §112

> ...because the specification...does not reasonably provide enablement for methods which are limited to the detection of a polymorphism at position 1388 of SEQ ID NO:1 [*sic*, 2]. Furthermore, the specification does not provide enablement for methods in which a polymorphism is diagnosed and then a PDH drug is administered (page 4 of the Office Action).

The Examiner asserts on pages 5-6 of the Office action:

> In particular, the specification teaches a polymorphic site at position 1388 of SEQ ID NO:2, in the 3′ untranslated region of the PDH E1α gene. The specification is silent with respect to the effect of this polymorphism on the biological activity of the PDH E1α gene. The specification does not disclose any relationship between the presence of this polymorphism [and] a change in the activity or expression of the PDH E1α subunit or between the presence of a particular allele of this polymorphism and any particular disease state or physiological condition.

Applicants wish to point out that the 3′ UTR of a gene affects a variety of different operations, including RNA processing (for example, cleavage and polyadenylation of the primary transcript), mRNA stability, mRNA localization, and translation efficiency. A polymorphism in the 3′ UTR of a gene potentially can affect any one or more of these processes. For example, RNA stability plays an important role during differentiation, development, and biogenesis of specialized cells and is also crucial to maintaining normal functions of individual cells and the organism as a whole. One of the most studied *cis*-acting elements of the 3′ UTR is the AU-rich element (ARE), a known destabilizing element found in a variety of short-lived mRNAs, including certain cytokine, lymphokine, and growth factor mRNAs. Engineering an AU sequence into a normally stable mRNA has been shown to result in a dramatically decreased half-life of the mRNA (for example, see Shaw and Kamen, *Cell* 46:659-667, 1986; abstract enclosed). AREs range between 50 and 150 nt in length and represent a diverse range of AU-rich sequences with no single conserved consensus motif. At least 15 proteins have been

identified that can bind to AU- and U-rich regions, several of which proteins have been shown to specifically regulate mRNA stability. Thus, a polymorphism situated within a 3′ UTR may disrupt a *cis*-acting element or create an aberrant *cis*-acting element recognized by RNA-binding proteins. Alternatively, the polymorphisms can alter other RNA functions by interrupting a crucial RNA structure, such as a hairpin.

Mutations in the 3′ UTRs of various genes have been implicated in a variety of diseases and disorders including cancer, inflammatory disease, thalassemia, and Alzheimer's disease. The molecular bases for these disorders can be attributed to a range of genetic defects including translocations, duplications, deletions, insertions, and point mutations, and the effects include decreased or increased mRNA stability and altered expression levels and/or mRNA localization (reviewed in Hollams *et al., Neurochemical Research* 27:957-980, 2002, copy enclosed). Given the knowledge in the field, as demonstrated above, one of ordinary skill in the art would indeed understand the myriad effects that a polymorphism in the 3′ UTR of the PDH E1α gene could have on the mRNA and consequent aberrant effects on gene expression and function. Furthermore, the molecular biology, genetic and biochemical techniques required to determine the effect of the polymorphism on RNA stability or gene expression are well known in the art, and thus it would not require undue experimentation to determine such an effect and then further link it to a physiological (disease) effect.

The Examiner states on page 8 of the specification,

> The specification does not provide any guidance as to how the polymorphism at position 1388 of SEQ ID NO:2 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug.

While not acquiescing in this ground for rejection, Applicants have canceled claim 8. New claim 17 is directed to a method of treatment that includes correlating a therapeutic effect of an agent with the identity of the nucleotide at the polymorphic site. The claimed method does not require prior knowledge of the correlation. Indeed, it can be used as a means of gathering such information, much as a screening assay is used to gather new information about a test agent. Applicants believe the presently claimed method to be fully supported in the specification, and

therefore respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

35 U.S.C. §102(b)

The Examiner rejected claims 1 and 2 under 35 U.S.C. §102(b) as being anticipated by Koike *et al.* (*Gene* 93:307-311, 1993). According to the Examiner,

> Koika *et al.* teach a method for the diagnosis of a polymorphism in a PDH E1α gene in a human which comprises determining the sequence of the nucleic acid of the human at position 1388 of SEQ ID NO:1, and determining the status of the human by reference to polymorphism in the PDH E1α gene (page 11 of the Office action).

Claims 1 and 2 have been canceled. New claims 11-16 and 21 are directed to methods of determining the presence or absence of a SNP in a PDH E1α gene and include the step of determining the nucleotide sequence in a sample obtained from a human having or at risk for having a PDH-mediated disease. Koika *et al.* did not disclose obtaining a sample from such a person. As the new claims are not anticipated by Koika *et al.*, Applicants request that the rejection under 35 U.S.C. §102(b) be withdrawn.